

Safety Evaluation of IV-administered BBP-812, an AAV9-based Gene Therapy for the Potential Treatment of Canavan Disease, in Mice and Juvenile Cynomolgus Macaques

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David Scott



I am a shareholder and employee of BridgeBio Pharma Inc, the parent company of Aspa Therapeutics

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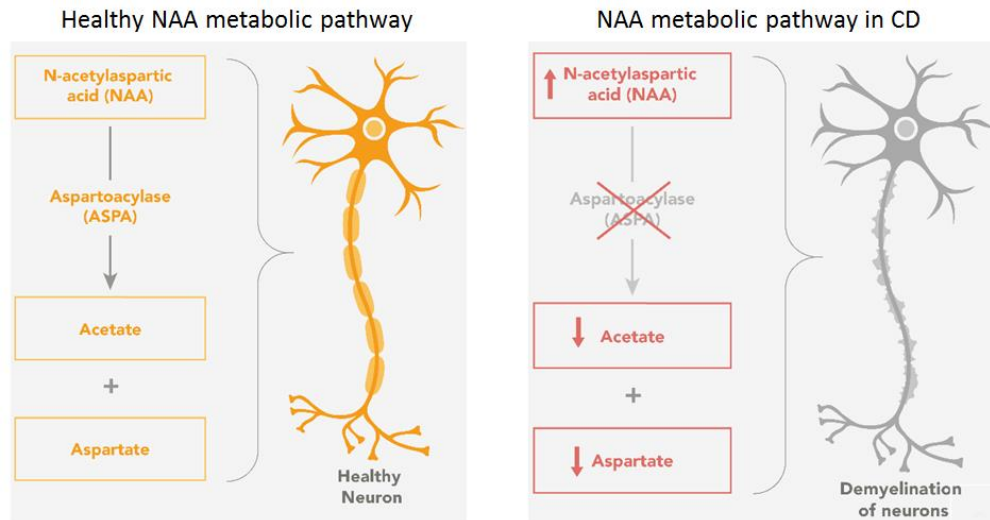
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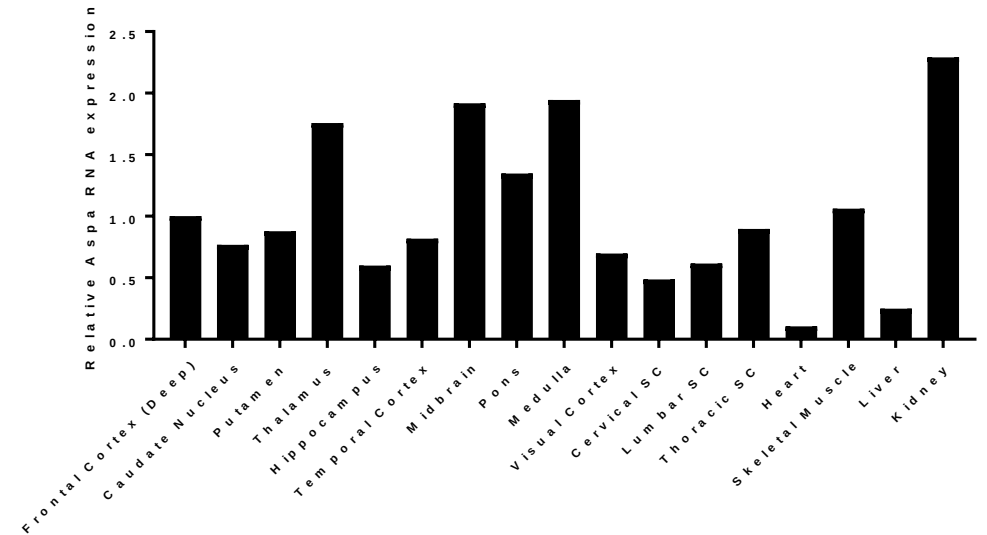
BBP-812 is being developed as a potential therapy for Canavan disease

- Canavan disease is characterized by a loss of Aspa expression and a systemic build up of N-acetylaspartic acid (NAA).
- In the presence of elevated NAA, neuronal demyelination occurs leading to progressive psychomotor regression.



- There are currently no approved therapies that target the underlying cause of Canavan disease.

- Aspa is expressed throughout the body and is enriched in deep, white matter regions of the brain



- BBP-812 is an AAV9-based gene therapy encoding the human Aspa gene being developed as a potential treatment for Canavan disease

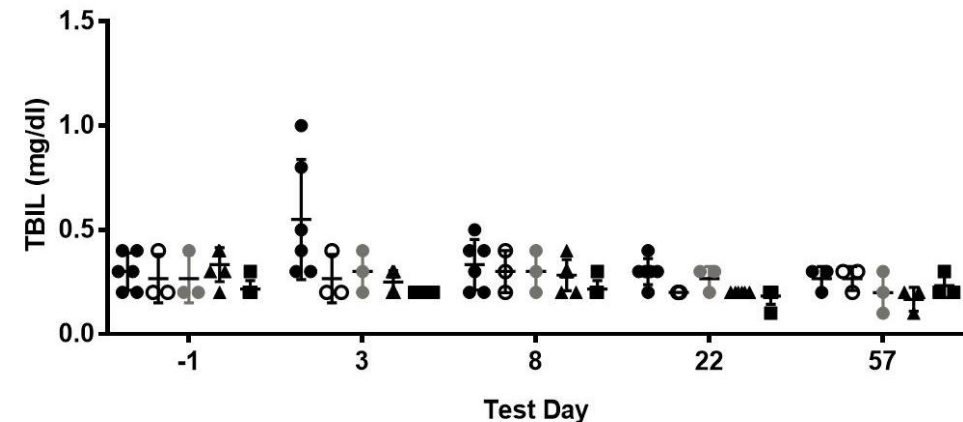
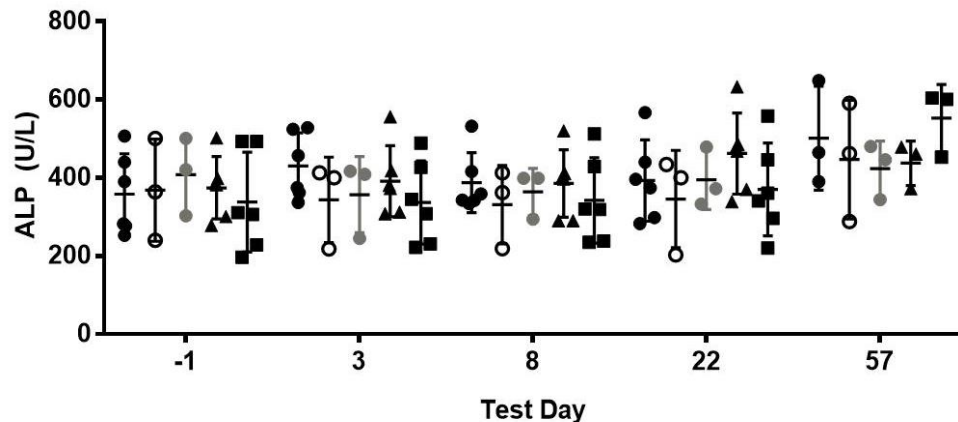
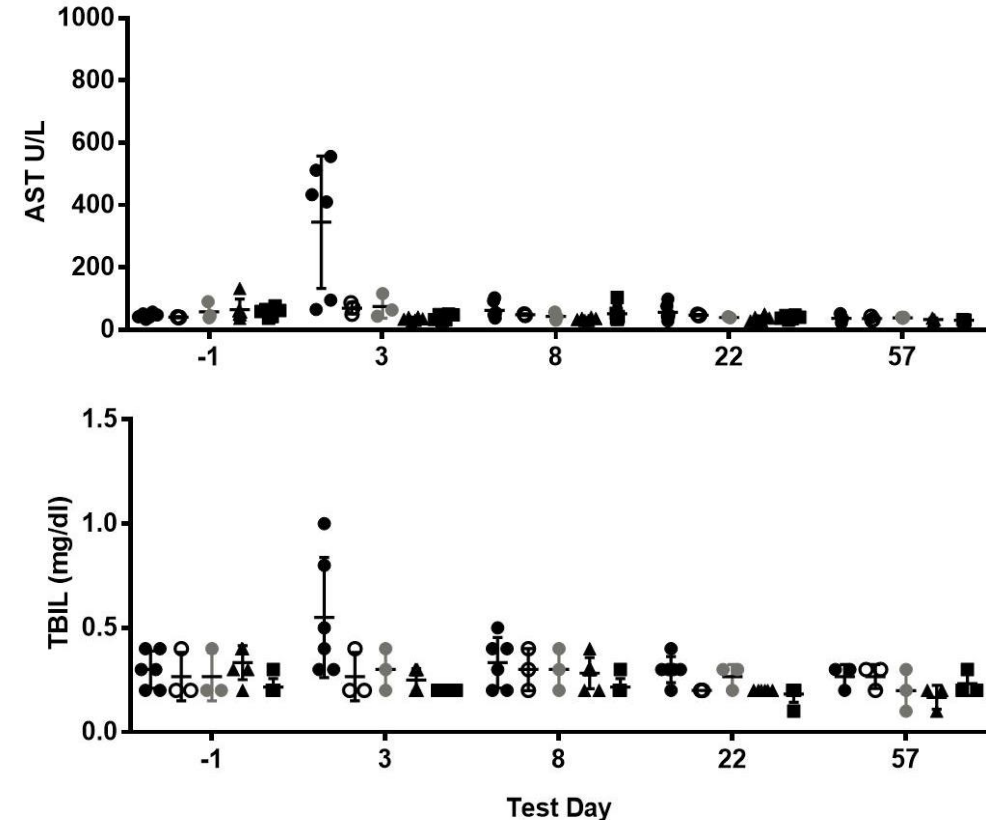
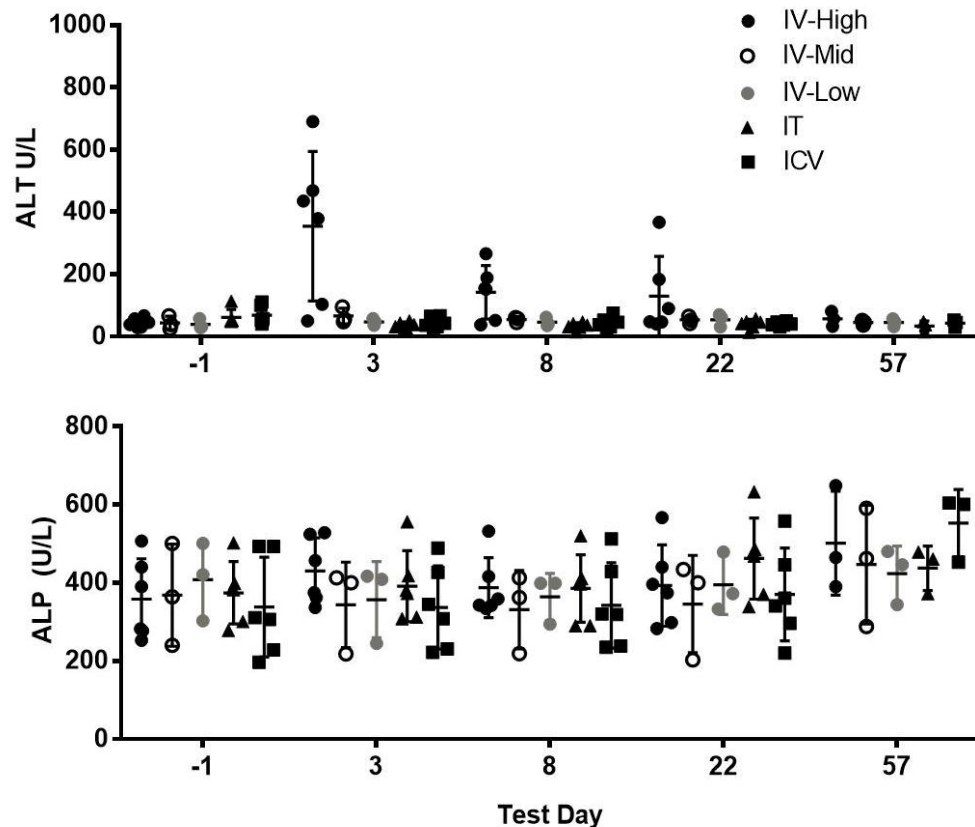
Evaluation of safety and biodistribution of BBP-812 in juvenile cynomolgus macaques

Group	Vector	Group size	ROA	Dose Level	Dose/kg or brain	3 week necropsy	8 week necropsy
1	BBP-812	N = 3	IV	Low	3.18×10^{13} vg/kg		N = 3
2		N = 3	IV	Mid	1.15×10^{14} vg/kg		N = 3
3		N = 6	IV	High	3.18×10^{14} vg/kg	N = 3	N = 3
4		N = 6	ICV	High	8.98×10^{12} total	N = 3	N = 3
5		N = 6	IT	High	8.98×10^{12} total	N = 3	N = 3
6	Vehicle	N = 4	ICV/IT	-	-	N = 2	N = 2

~2kg, 2-2.5yo

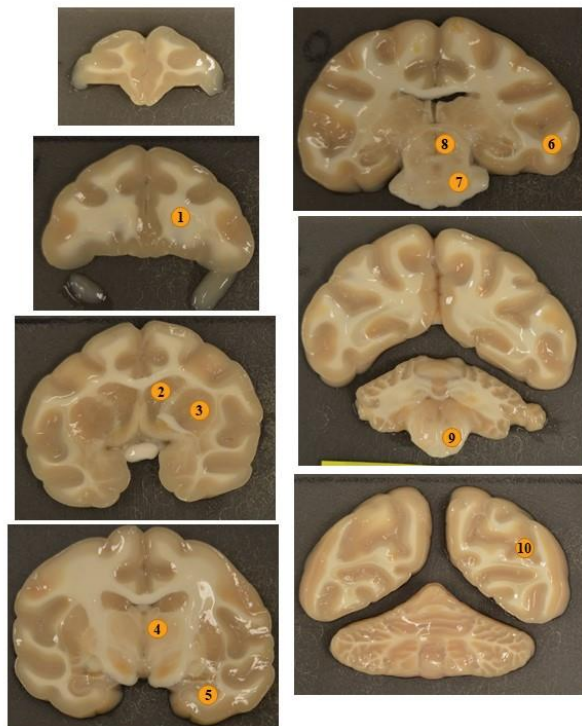
- Hematology and Clinical pathology
- Biodistribution
- Immunological response to capsid and transgene
- Full histology panel with focus on CNS

BBP-812 induces a transient increase in transaminase levels without impacting other markers of hepatotoxicity



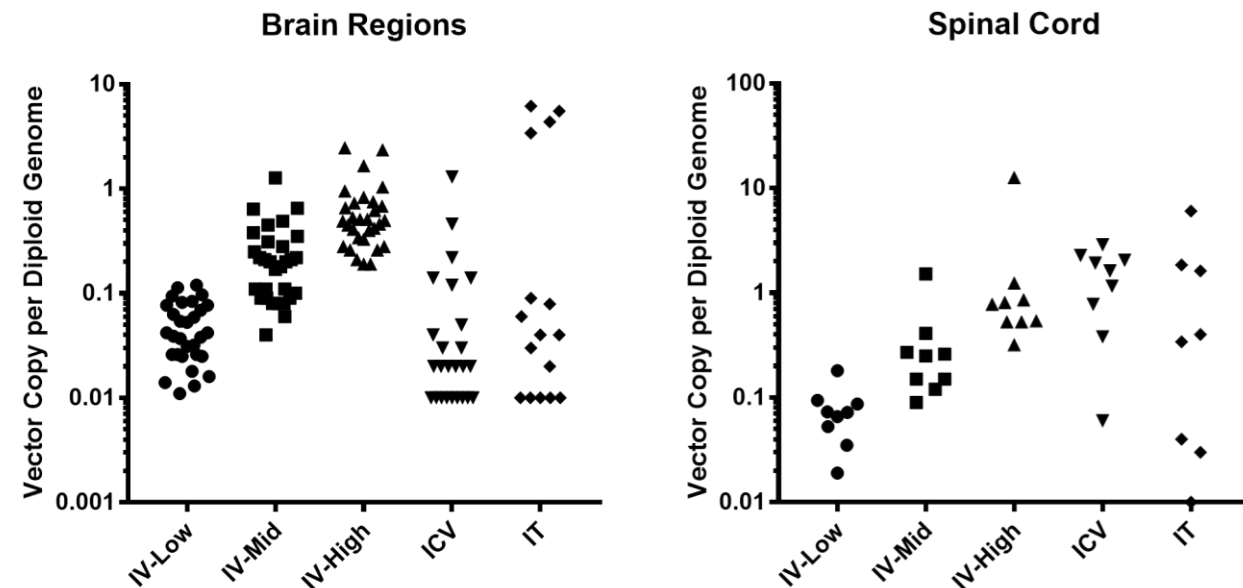
- No thrombocytopenia
- No coagulopathies

IV-administration of BBP-812 provides superior biodistribution to brain regions when compared to ICV and IT



Sample	Tissue
1	Deep frontal cortex
2	Caudate nucleus
3	Putamen
4	Thalamus
5	Hippocampus
6	Temporal cortex
7	Midbrain
8	Pons
9	Medulla
10	Visual cortex
11	Cervical Spinal Cord
12	Lumbar Spinal Cord
13	Thoracic Spinal Cord

Analysis at Day 57



IV-administration of BBP-812 was not associated with adverse histopathological findings including in DRG

Summary of analysis per animal:

- Full panel of peripheral tissues.
- Brain was analyzed at 15 levels.
- Spinal Cord was analyzed at four levels.
- At least two dorsal root ganglia and associated spinal nerve roots from each of four spinal cord levels

Key Findings:

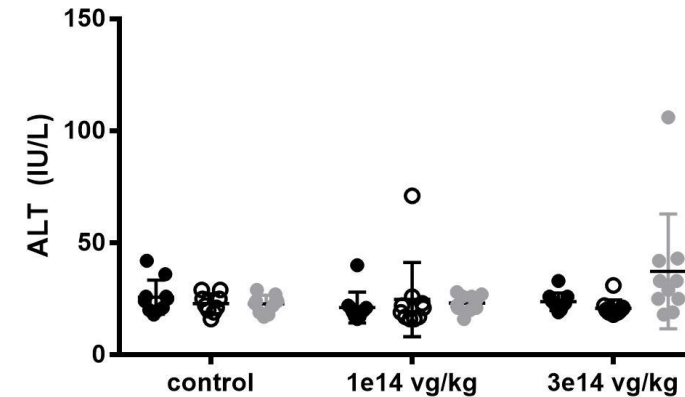
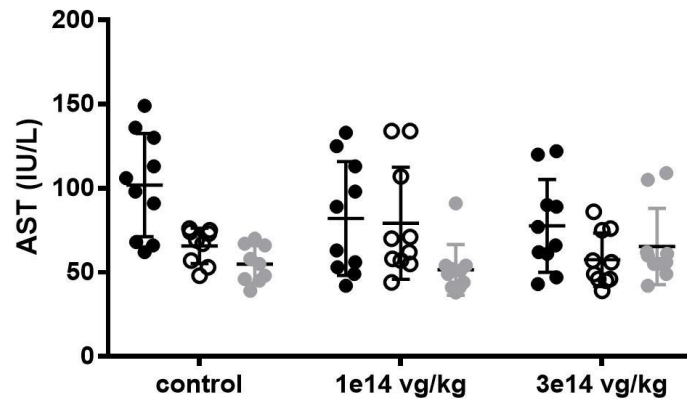
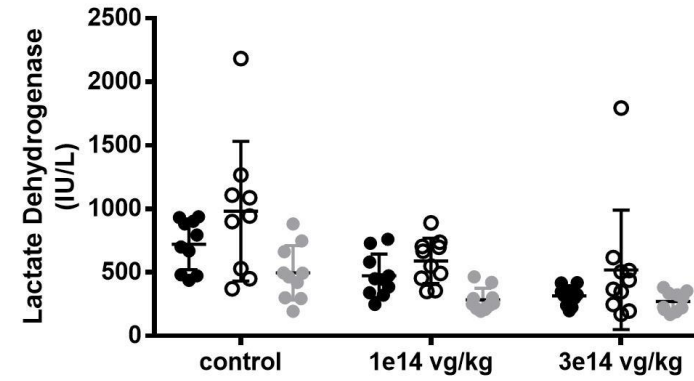
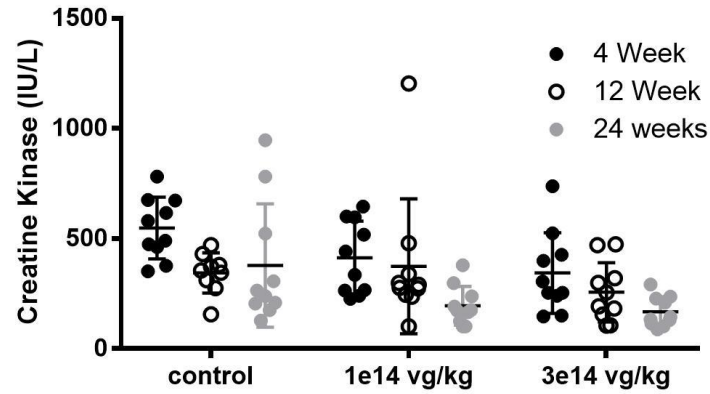
- Liver analysis demonstrated portal infiltrates and/or increased cellularity in high dose IV group which was minimal (Grade 1) and not considered adverse.
- There was a minimal (Grade 1) increase in cellularity observed in 4 of 48 DRG analyzed from highest dose IV-treated animals.
- **No evidence of axonopathy or neuronal degeneration associated with IV-administered BBP-812**

GLP Toxicology assessment of BBP-812 in wild type C57Bl/6 mice

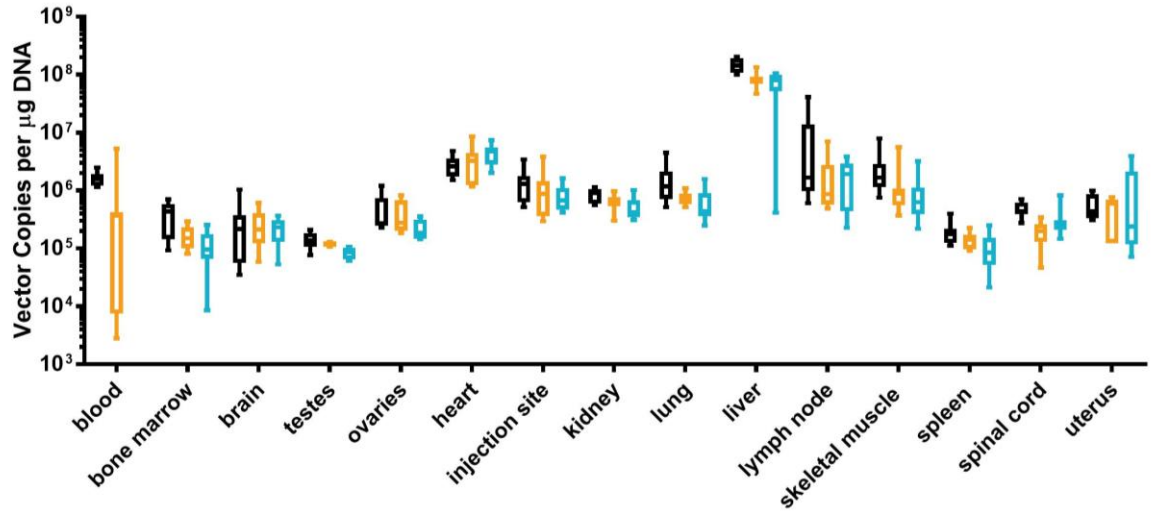
Group	Vector	ROA	Dose Level	Dose/kg or brain	Necropsy Timepoints
1	BBP-812	IV	High	3.0×10^{14} vg/kg	4, 12, and 24 weeks
2		IV	Low	1.0×10^{14} vg/kg	4, 12, and 24 weeks
3	Vehicle	IV	-	-	4, 12, and 24 weeks

- Hematology and Clinical pathology
- Biodistribution
- Immunological response to capsid and transgene
- Full histology panel

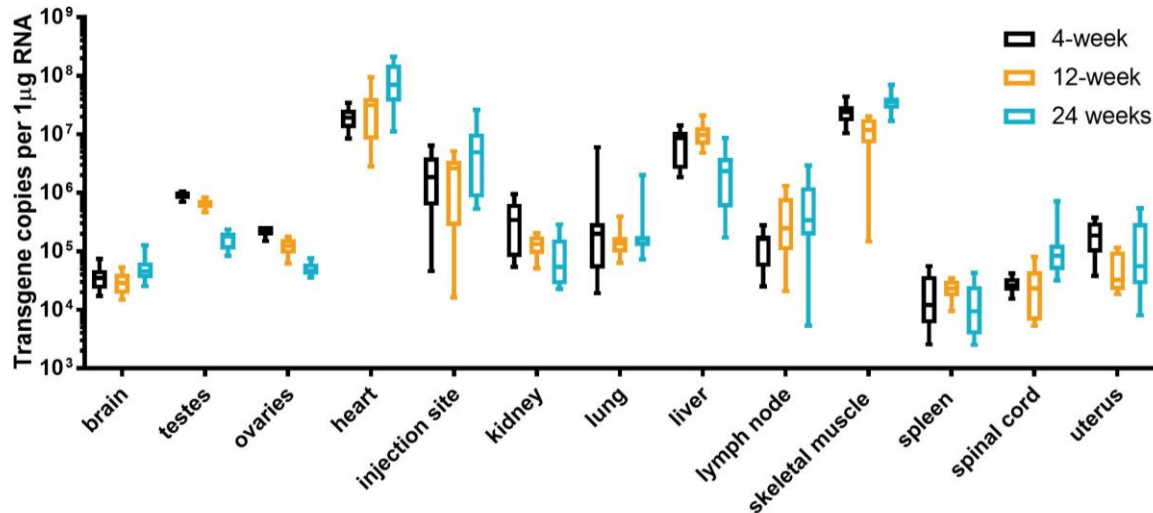
IV-administration of BBP-812 was not associated with any adverse changes in hematology or clinical chemistry



IV-administration of BBP-812 provided broad and persistent biodistribution



- Vector detected in all tissues assessed with a gradual decline over time
- Transgene RNA detected in all tissues assessed and remained steady throughout study

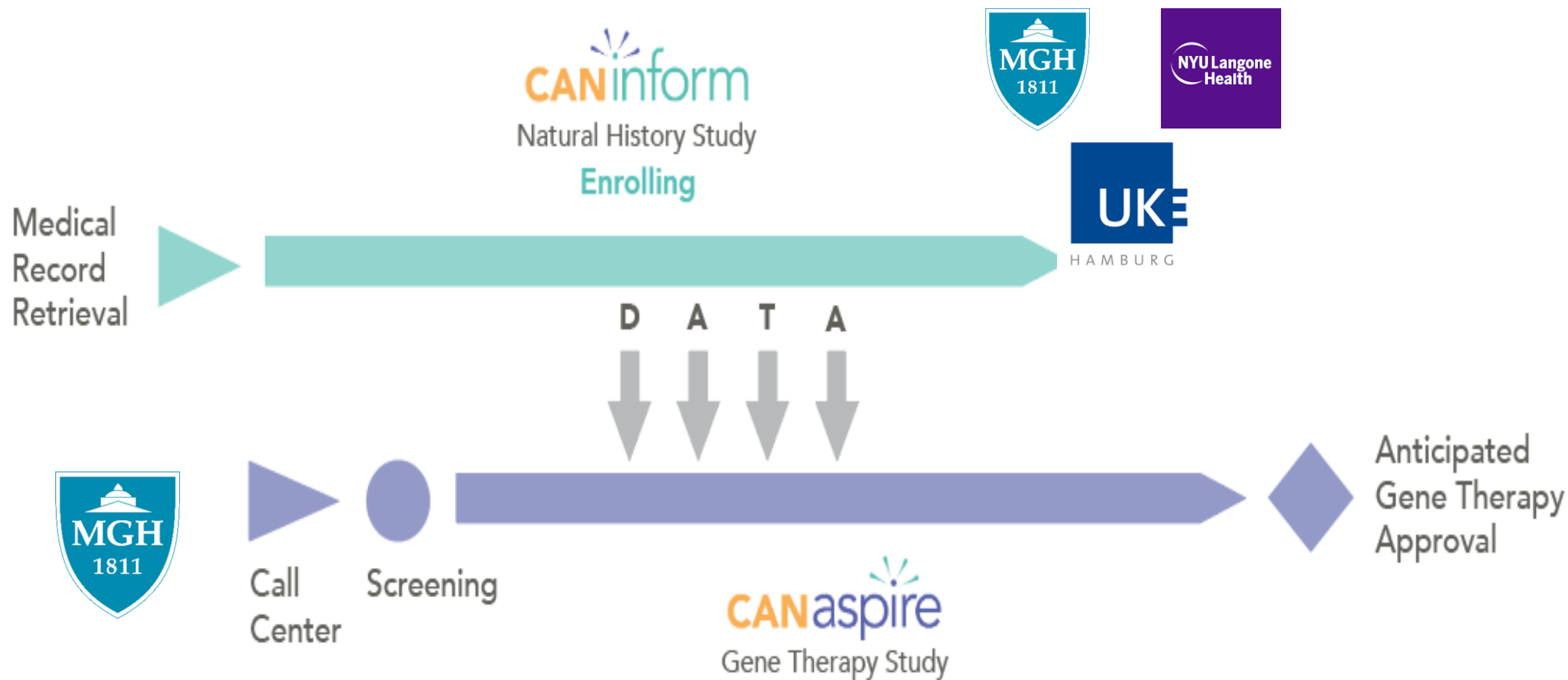


Conclusions

- Transient elevation in AST/ALT in NHPs returned to baseline without intervention and a similar increase was not observed in mice.
- IV-administration resulted in broad CNS biodistribution to deep brain regions that was superior to IT or ICV administration.
- No adverse histopathological findings were observed in either NHPs or mice at any dose.
- NOAELs were determined to be 3.18×10^{14} vg/kg in NHP and 3.0×10^{14} vg/kg in mice.
- Results support the continued clinical development of BBP-812 for the treatment of Canavan disease.

ASPA CLINICAL PROGRAM OVERVIEW

treatcanavan.com



Acknowledgements

Bridge Bio Gene Therapy Team



Dominic Gessler
Guangping Gao